MULTIFUNCTIONAL OPTO-ELECTRONIC BIOCHIP DETECTION SYSTEM

BACKGROUND OF THE INVENTION

Field of Invention

[0001] The present invention relates to a multifunctional opto-electronic detecting technology. More particularly, the present invention relates to a multifunctional opto-electronic biochip detection system, suitable for use in production quality test of biochip and detection of biochemical reaction signal.

Description of Related Art

[0002] Conventional biomedical or chemical sensor are usually comprised of two parts. One is molecular recognition element and another one is signal generator or converter. Under this mechanism, a bio-sensor mainly includes a piezoelectric crystals and a fiber optical immunosensor.

[0003] the conventional technologies of for testing a biochip include resonance mirror (RM), surface plasmon resonance (SPR) detection, X-ray photoelectron spectroscopy, scanning probe microscopy, and scanning tunneling microscopy. These technologies have their advantages. However, the X-ray photoelectron spectroscopy employs radiation for test. Even though the scanning probe microscopy technology has good atom resolution, it may cause a damage on the surface bio-molecules and change its activity when the technology is applied to detect bio-molecules, resulting in limited use. Moreover, it still has other technologies, such as ultrasonic excitation, wave guide

method and so on. In general, each of the above technologies has its different detection mechanism, and the associated chip design is also different. For example, resonance mirror technology needs an agitator to satisfy the requirement of testing condition, and a design concept of the detection container is completely different from a design concept of the chip used in the surface plasmon resonance detection. Therefore, the conventional detector is usually restricted into specific machine associating with specific detecting technique. Currently, it is still absent for a detection system, which can effectively integrate multiple detecting functions to satisfy the great amount of need on the detecting platform in the current biomedical technology.

[0004] The opto-electronic detecting technology in the various related detecting technologies have been approved to be most useful technology in the field of biochip technology. This conclusion is made according to the observations from the biomedical field on the opto-electronic detection technology at a few concerning points: (1) non-contact and non-invasive, which would not affect the tested sample, and (2) high sensitivity, wide bandwidth, and small probe volume, which allow the great need still to be satisfied when the biochips or test samples are in great shortage for the current situation in the whole word. However, the function of the opto-electronic detector has strong relation with the system of chip mechanism. In developments for past years, most of detector are still using the chip system which is based on the enzyme-linked immunosorbent assays (ELISA) mechanism, in which the assays are distributed on the biochip in an array manner. Through the signals from the assays are detected or read by an analysis system, a reaction chain including several different reactions can be simultaneously detected, and then a sieving procedure can be performed. This detecting mechanism asso-

ciating with the biochip has been widely used in the DNA research. Particularly in the past few years, a technology of biomolecular interaction analysis (BIA) based on the bio-reaction mechanism has been developed. The BIA technology includes affixing assays on a surface of the sensing chip by a specific arrangement. A biochemical reaction is triggered by using interaction of continuous micro fluid with the sensing chip. Then, an signal detecting system, usually in optical manner, is used to read out signals for forming the sensorgram.

[0005] The detecting foundation theory is continuously updated in the recent years. For example, B. Liedberg et al. in 1983 had introduced the detecting system based on surface plasmon resonance effect. The resolution can achieve to the level of ng/ml. H. Yang et al. in 1994 had reported a technology based on electrochemistry fluorescent detecting system, which technology has resolution ranging from 10 pg/ml to 5 ng/ml. Brain Trotter et al. had published in Optical Engineering at May, 1999 about a technology of optical immunosensor assay detection based on the mechanism of fixed-polarizer ellipsometry, which technology shows an experimental result better than 4 pg/ml. This is a practical application of fixed-polarizer ellipsometry in biochemical field, and the fixed-polarizer ellipsometry technology is foreseen to be a very useful detection tool in the biochemical field. From the foregoing research reports, it is expected to have more applications for the fixed-polarizer ellipsometry technology on the biochip.

[0006] On the other hand, the biomedical detection function should includes both the quantitative detection and the qualitative observation. The signal detection and the three-dimensional image displaying are very essential. The further conventional

technology of the current technology usually use optical microscopy, which has insufficient resolution. Scanning electron microscope (SEM) and atomic force microscope (AFM) may cause a damage on the assay sample, in which the samples need to be pre-processed or be operated in a vacuum environment, causing very inconvenient operation. Therefore, optical technology for the test sample could also be a trend in the next generation of biomedical detecting technology.

[0007] Moreover, the conventional optical system is designed with a single angle measurement and a signal incident angle. This can not allow the image to be precisely displayed

SUMMARY OF THE INVENTION

[0008] The invention provides an opto-electronic biochip system which is designed with a novel optical mechanism associating with advanced optical detecting principles, so as to achieve high resolution and be high repeatable.

[0009] The invention provides an opto-electronic biochip system which uses an optical interferometer with sufficiently high resolution to capture dynamic and static information of the bio-molecules, and uses the optical tunneling effect, confocal scanning, and optical coherence tomography (OCT) scanning technology, so that a micro-change on the surface of the tested sample can be well observed. Moreover, an advanced optical representation with image reconstruction technology is employed in design to achieve 3-D image display.

[0010] The invention provides a multifunctional opto-electronic biochip system, satisfying needs for the overstriding platform detection as shown in FIG. 1. The func-

tional system is shown in FIG. 2, so that all the sub-functional units are effectively integrated, wherein some optical paths are commonly used. With respect to different detecting platforms and the corresponding detection mechanism, functions for signal detection and opto-electronic transformation have been introduced. All the optical detection function can also be effectively integrated into a micro-electric system. The invention is suitable for use in biochip developing stage or biochip production stage, and is a complete multifunctional biochip platform.

[0011] In the invention, a multifunctional opto-electronic biochip detection system is an optical system which includes four advanced optical detecting theories : ellipsometry (a first subsystem), confocal scanning theory (a second subsystem), evanacent wave theory (a third subsystem), and interferometry (a fourth subsystem). Each subsystem has a commonly used optical path and in combination with an optical member that has ability to receive light with variable incident angle. The opto-mechanical unit can be switched according to different detection theory, so that eight function, including the ellipsometer, can be achieved.

[0012] the subsystem, such as the ellipsometer can be used in development and production of biochip. The function includes measuring refractive indices and thickness of coating layer, such as gold film or protein film, on a substrate during production. The ellipsometer is also a necessary tool in fabrication process of lithography and etching during developing the biochip carrier. The ellipsometry can also associate with an optical member with variable incident angle, so that the parameters for the multi-layer coating film can be analyzed, and it therefore is useful for detection of more complicate biochemical reaction. A laser Doppler interferometer can be used to measure the dy-

namic interaction between protein chip, antibody, or antigen. The laser Doppler interferometer has a dynamic bandwidth of a level of 100 MHz for detecting a vibration, which is equivalent to a vibration of 10^{-10} meter, and can be used for insitu detection through associating with ultrasonic technology that triggers the combination of antibody-antigen. As a result, the dynamic properties between bio-molecules can be analyzed.

[0013] The SPR configuration unit includes not only the function of using SPR amplitude to measure critical angle, like what the conventional commercial system technology has done, but also the function of determining the critical angle by using double exciting on SPR and measuring the phase. As a result, the sensitivity can be improved several times. The system of the invention further includes a combination of precise paraboloidal mirror with a stepping motor or at least a DC motor, so as to achieve a precise control of the incident angle, whereby the precision of measurement on the critical angle can be improved by at least 10 times more than conventional SPR. The object of function for measuring amplitude in built-in multifunctional optoelectronic biomedical detector and the surface plasmon resonance is to provide the optoelectronic detection function with novel, instant, precise, and high resolution. Particularly, when the invention is applied to measurement in biology, medicine, and chemical reaction, suitability of BIA and ELISA can be both considered. The biochip for any type of above system configurations can be put on a platform with double precision control. A laser light is incident on metal and dielectric interface, so as to generate a surface plasmon wave. A variable incident angle optical set is used to control for obtain a total interval reflection. As the incident angle of the total reflection is changed, the am-

plitude and intensity of the generated surface plasmon wave is changed also. When the resonant state is achieved, it is called the SPR.

[0014] In order to achieve the foregoing functions, the optical system of the multifunctional opto-electronic biochip system of the invention needs to associate with a biochip having a three-layer structure that includes bio-molecules such as protein molecules or DNA, a metal film such as gold or silver with a thickness of about 40-60 nm, and a substrate such as PMMA, glass or silicon material. The incident light is led to the biochip, so as to generate the surface plasmon wave for measuring the optical parameters produced by the surface plasmon wave, so that the variation of the refractive index of reaction assay can be real-time measured, and the corresponding concentration variation of reaction and a thickness of bio-molecules can also be computed out.

[0015] The interference microscopy configuration has function to directly measure the surface topology of the biochip. If the material is uniform, it stands for a surface configuration of the tested sample or the bio-molecules. This function is equivalent to the interference microscopy used in semiconductor fabrication. The needed parameters used to design a biochip can be totally controlled under the system of the invention. The invention further combined the measurement of ellipsometer and the function of backward calculation into the interference microscopy, so that the practical surface configuration for the non-uniform surface can be measured. This application function is essential while the chip is under developing, quality control, and production.

[0016] The configuration of photon scanning tunneling microscopy uses energy dissipation of the evanescent wave due to total interval reflection to detect the surface configuration of the tested body, wherein the energy dissipation is proportional to the

power index of the distance between the tested body and the total reflection plane. In this manner, the height can be measured with a precision up a level of 10^{-10}.

[0017] The multifunctional opto-electronic biochip system of the invention also includes functions of optical coherence tomography scanner and confocal microscopy. The two functions are the important tools in the biomedical technology for researching and detecting. By means of the variable incident angle optical set and the optical CT scanning technology, the biobody can be observed by section, where a technology of random transformation to reconstruct image is used, so that the spatial resolution is improved. This is very helpful for three-dimensional image reconstruction between bio-molecules, or the combination of the bio-molecules and the biochip surface.

[0018] In addition to the foregoing function of built-in multifunctional opto-electronic detection system, the invention also disclose how the system to be set up two sample platforms. One platform is designed to have a path of about 10 cm with precision of micrometer. This platform can be used for scanning on the whole biochip area. Another platform is designed to have a path of about 10 microns with precision of nm. This platform can be used for scanning on ultra precision surface configuration and property of biochemical reaction. In further combination with local spatial scanning, the probe volume of the optical detecting technology can be further reduced, so as to improve spatial resolution. Moreover, functions of the multifunctional opto-electronic medical detection of the invention can be performed under BIA and ELISA system for detection, whereby multiple testing sites can be tested in parallel and the volume of tested sample is greatly reduced, time and cost for testing and fabrication of biochip can be greatly reduced.

[0019] It is to be understood that both the foregoing general description and the following detailed description are exemplary, and are intended to provide further explanation of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The accompanying drawings are included to provide a further understanding of the invention, and are incorporated in and constitute a part of this specification. The drawings illustrate embodiments of the invention and, together with the description, serve to explain the principles of the invention. In the drawings,

[0021] FIG. 1 is a drawing, schematically illustrating a layout and light path of the multifunctional opto-electronic biomedical detection system, according an embodiment of the invention;

[0022] FIG. 2 is a drawing, schematically illustrating a system configuration of the multifunctional opto-electronic biomedical detection system, according an embodiment of the invention;

[0023] FIG. 3 is a drawing, schematically illustrating a conventional ellipsometer;

[0024] FIG. 4 is a layout drawing, schematically illustrating a first subsystem configuration with phase modulation ellipsometry polarizing function in the multifunctional opto-electronic biomedical detection system, according an embodiment of the invention;

[0025] FIGs. 5A-5B are drawings, schematically illustrating a conventional confocal scanning theory;

[0026] FIG. 6 is a layout drawing, schematically illustrating a second subsystem configuration with confocal image scanning function in the multifunctional opto-electronic biomedical detection system, according an embodiment of the invention;

[0027] FIGs. 7A-7B are drawings, schematically illustrating a conventional optical configuration for theory of total reflection evanacent wave excitation;

[0028] FIG. 8 is a layout drawing, schematically illustrating a third subsystem configuration with confocal image scanning function in the multifunctional opto-electronic biomedical detection system, according a first embodiment of the invention;

[0029] FIG. 9 is a layout drawing, schematically illustrating a third subsystem configuration with confocal image scanning function in the multifunctional opto-electronic biomedical detection system, according a second embodiment of the invention;

[0030] FIG. 10 is a layout drawing, schematically illustrating a third subsystem configuration with photon tunneling scanning microscope in the multifunctional opto-electronic biomedical detection system, according a third embodiment of the invention;

[0031] FIG. 11 is a drawing, schematically illustrating a conventional Michaelson interferometer;

[0032] FIG. 12 is a layout drawing, schematically illustrating a fourth subsystem configuration with phase interference technology in the multifunctional opto-electronic biomedical detection system, according the embodiment of the invention;

[0033] FIG. 13 is a layout drawing, schematically illustrating a fourth subsystem configuration with optical coherence tomography technology in the multifunctional

opto-electronic biomedical detection system, according the embodiment of the invention;

[0034] FIG. 14 is a layout drawing, schematically illustrating a fourth subsystem configuration with Doppler laser interference technology in the multifunctional opto-electronic biomedical detection system, according the embodiment of the invention; and

[0035] FIG. 15 is a layout drawing, schematically illustrating an integration of the third and the fourth subsystem configurations, wherein the phase detection of the surface plasmon wave under the interferometer can be performed, according another embodiment of the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

First Embodiment

[0036] A first subsystem about the theory of ellipsometry is depicted in the following. The conventional structure for a ellipsometry is shown in FIG. 3. In the invention, a multifunctional opto-electronic biochip detection system first includes a first subsystem which follows a conventional PMSA ellipsometry and further includes a novel design of optical configuration, so that the ellipsometry can be used with variable incident angles. The multifunctional opto-electronic biochip detection system, four subsystems commonly use the light path of the first subsystem, so that the other units can be easily switched, thereby to achieve the function of the subsystem designed with its associated principle. The subsystem includes following units.

[0037] A linear polarizing light source member used to provide the needed polarizing light source for the invention.

[0038] A phase modulation unit has function of phase modulation to change the polarizing state of the light.

[0039] A reference optical analyzing unit includes a non-polarizing optical beam-splitter, an analysis plate and two photodetectors.

[0040] A variable incident angle optical set has a quasi-paraboloidal reflective mirror, a quasi-spherical reflective mirror, and a uniaxial displacement stages that can be controlled by a feedback manner and carry a prism set. The function of variable incident angle optical set is used to adjust the angle of incident light beam onto the biochip.

[0041] An optical signal analysis unit has an analyzer and a photodetector.

[0042] A microscope lens set includes a camera apparatus having a high power lens set and a CCD array, so as to monitor the reaction situation of bio-molecules on the surface.

[0043] The variable incident angle optical set of the subsystem of ellipsometer in the multifunctional opto-electronic biochip detection system can cause the measuring light to transverse back along the same light path to the test sample, and enter the optical signal analysis unit. The optical signal analysis unit can let the measuring light pass the tested sample twice, resulting in improvement of precision and sensitivity for the ellipsometry. Moreover, with respect to different needs, the optical signal analysis unit can switch the measuring light, which is incident to the tested sample, into a line measurement of a point measurement. Furthermore, the incident angle of the measuring light can be precisely controlled and adjusted the incident direction. This a breakthrough comparing with the conventional issues being unable to easily and precisely change the

incident angle. Further still, the size of the ellipsometer is greatly reduced, so that it can be applied to various biomedical real-time detection.

[0044] In the foregoing descriptions, the polarization lens set can include a single band visible light, an attenuator to modulate light intensity, and a linear polarization element. The light source can be a light emitted diode or a laser diode. The linear polarization element can include a linear polarizer, a polarizer, or any element to polarize the light.

[0045] In the foregoing, the phase modulation unit having the function to change phase includes a compensator, a liquid crystal phase modulator or an optical pick phase modulator, so that various polarizing state is provided.

[0046] In the foregoing, the variable incident angle optical set can include a penta prism or a triangular prism. It can even include a reflective mirror to adjust the incident angle of incident light onto the biochip. The foregoing paraboloidal mirror, and spherical reflective mirror can be alternatively replaced with a parabolic-profile cylindrical mirror and circular-profile cylindrical mirror, so that the measuring light is to be linear. The quasi-paraboloidal reflective mirror and the quasi-spherical reflective mirror can be properly arranged, so as to have focusing power and transmitting the dielectric material. The paraboloidal mirror also includes, for example, a parabolic rod mirror and the spherical mirror also includes, for example, cylindrical mirror.

[0047] In the foregoing, the photodetector of the reference optical analyzing unit can include a photodiode or a linear array CCD.

[0048] FIG. 4 is a layout drawing, schematically illustrating a first subsystem configuration with phase modulation ellipsometric function in the multifunctional opto-electronic biomedical detection system, according an embodiment of the invention.

[0049] In FIG. 4, a laser light 101 emits a measuring light beam 100, which transverses through an attenuator 102, a reflective mirror 103, and a non-polarizing beam-splitter 104, and then is split into two light beams 110, 120. The light beams on the light path 120 is reflected by a reflective mirror 105 and transverses through a linear polarizer 106, a phase modulator 2, and a reference optical analyzing unit 3, to complete the reference light path. The light beam on the light path 110 is reflected by the non-polarizing beam-splitter 104 and transverse through a polarizer 106, the phase modulator 2, to form the sampling light beam and enter a variable incident angle optical set 6. The light beam enters tested sample on the biochip 12 at the specific detection site. The light beam is back and forth incident on biochip for twice, and then a back light path transverse back along the light path of forwarding sampling light beam 110, and then reaches to non-polarizing beam-splitter 4, 7. The back light beam is split by the non-polarizing beam-splitter 7 into two light beams 113, 114. The light beam 113 transverses through the analyzer 1101 and is propagated the photodetector 1104. In addition, an observing light beam 114 is propagated to the microscope lens set 8.

[0050] In the first embodiment, the system is under programmable control to separately process capturing signals, control the incident angle, and compute the index of reflection for the tested sample, wherein the main control program is executed by a graphic manner. The laser light 101 can be activated by issuing a TTL modulation signal from the main program to the laser driver, so as to modulate the detecting signals.

Moreover, in order to use the feedback control system to control the liquid crystal phase modulator 2, the light beam 100 is split into a referencing light beam and sampling light beam by the beam-splitter 104. After the referencing light beam and sampling light beam are led to the linear polarizer 106 and the phase modulator 2, then the light intensity and polarization state of the referencing light beam 120 are used as a reference for comparing with the light intensity and polarization state of the sampling light beam 110. The detail about signal processing is using a beam-splitter 301 to split the referencing light beam 120 into two light beams 121, 122. The light beam 121 is directly propagated to the photodetector 304, and the other light beam 122 is propagated to the photodetector 303 through an analyzing pate 302. At this time, the system main program read the light intensity from the photodetector 303, 304 through the signal fetching card 305, 306, that include optical beam expanders 305, 306. The measured light intensities can be either used for control the liquid crystal in feedback manner, or providing for the measuring analysis.

[0051] the sampling light beam 110 enters the variable incident angle optical set 6, where the refracted light beam 111 and the light beam 110 normal incident to the penta prism 601 are perpendicular to each other. The perpendicular condition is assured by the property of the penta prism 601. The refracted light beam 111 can also serve as a horizontal incident beam for the concave paraboloidal reflective mirror 602. In this embodiment, the main program can control the uniaxial displacement stage 605, which is used to hold the penta prism 601, through a motion control card (MCC) 604 and limit switches 607, 608. When the motion is moving back-and-forth along the Z-axis, the incident angle onto the sample of the light beam 1111 can therefore be controlled. The

function of the variable incident angle optical set 6 is to allow the light beam 1111 to propagate through the substrate of the biochip 12 and reach to a measuring point on the coated metal film on the substrate, whereby a reflective light beam 1112 of the sampling light beam. The light intensity of the reflection light beam varies as changes of the thickness of tested sampled on the biochip and the refractive indices, that is the size of the bio-molecules and the sample concentration. The reflected light beam transverses through the quasi-spherical reflective mirror 603 along the original incident light path, and transverses through the photodetector 1104. A measured signals are then obtained.

[0052] In this embodiment, the concave quasi-paraboloidal reflective mirror 602 and the concave quasi-spherical reflective mirror 603 are incorporated, whereby the reflection light beam 1112 of the sampling light beam can be normal incident onto the concave quasi-spherical reflective mirror 603. After reflection from the concave quasi-spherical reflective mirror 603, the incident light beam 1121 on the backward light path is formed. The light beam 1121 transverse along the light path of the light beam 1112 and enter the substrate 12 of the biochip. At the same measuring point, a reflection occur again. Thus, light intensity of the light beam 1122 on the backward light path has been changed for twice, resulting in improvement of the resolution.

[0053] In the embodiment, the microscope lens set 8 includes a lens set 801, a CCD array 802, and a frame-grabbing card 803 to have the function of camera. The microscope lens set 8 is used to observe and adjust the measuring point on the sliding plate. The observing light beam and the sampling light beam 110 are provided by the laser source 11, so that the system does not need extra light source. The microscope lens set 8 read the image at the measuring point through the frame-grabbing card 803.

The image can be instantly observed when it is connected to computer or monitor, and simultaneously serves as an autocollimator for the sampling light beam 110.

Second Embodiment

[0054] A second subsystem uses the confocal scanning theory is depicted as follows. FIGs. 5A and 5B are drawings, schematically illustrating a conventional confocal scanning theory. In the multifunctional opto-electronic biochip detection system of the invention, the first subsystem can be switched to include a beam expander, so as to expand the sampling area, and a focusing lens set is inserted before the photodetector with respect to signal analyzing unit. The focused light beam is led through a pinhole, whereby a confocal microscope is formed. The detailed light path and the layout of elements are shown in FIG. 6. The subsystem includes several unit as follows.

[0055] A linear polarized light source set includes a visible light source, an attenuator for modulating light intensity, and a linear polarization member. The light source is formed by, for example, light emitted diode (LED) or laser diode. The linear polarization member includes, for example, a dichroic linear polarizer, a linear polarizer, or a polarizing means for polarizing light.

[0056] A phase modulating unit having capability for modulating the phase includes a compensator, a liquid crystal phase modulator, or a photoelastic phase modulator. The phase modulating unit is used to produce a light with various polarization state.

[0057] An optical beam expander with a lens set is used to expand the area of the sampling point.

[0058] A referencing beam optical analysis unit includes an non-polarizing beam-splitter, an analyzer, and at least two photodetectors.

[0059] A variable incident angle optical set includes a quasi-paraboloidal mirror, a quasi-spherical reflective mirror, and a uniaxial displacement stage with feedback control for loading a prism set. The prism set includes, for example, a penta prism or a triangular prism, or even includes a reflector. Function of the variable incident angle optical set is to adjust an incident angle of the incident light beam onto an interface between the substrate of the biochip 12 and the coating metal film.

[0060] An optical signal detecting unit has at least a photodetector, a focusing lens set, and a pinhole set. The photodetector includes, for example, a photodioide or a linear array of CCD.

[0061] A microscope lens set has a lens set with high power, and an array of CCD, so as to serve as a camera that is used to monitor the reacting phenomenon of biomolecular interaction.

[0062] The multifunctional opto-electronic biochip detection system of the invention has the function of novel confocal microscope that is different from the conventional confocal microscope. The confocal microscope of the invention uses OBMorph structure to have design of variable incident angle. It is therefore that the section of sample is not limited to only the perpendicular direction. The novel confocal microscope can make a section on the tested sample from different angles, so that a 3-dimensional structure of image can be more precisely displayed.

[0063] The light path is described as follows. A measuring light beam 100 transverses through an attenuator 102, a reflector 103 and non-polarizing beam-splitter

104, so as to divide the measuring light beam 100 into two beams. One beam transverses along the light path 120 through a reflective mirror 105, a polarizer 106, a phase modulator 2, a referencing beam optical analysis unit 3, and then the light path is accomplished. Another sampling light beam transverses along the light path 110. After being split by the non-polarizing beam-splitter 104, the light beam transverses through the polarizer 106, the phase modulator 2, and the optical beam expander 804. The sampling light beam 110 enters the variable incident angle optical set 6, and then the light on the specific measuring points on the test sample on the substrate 12 of the biochip is secondly reflected. A backward light path 112 is along the original light path 110 but the traveling direction is backward. The backward light path 112 continuously transverses through the non-polarizing beam-splitters 4, 7 that splits the light beam into two beams 113, 114 again. The light beam 113 transverses through the analyzer 1101, the lens set 1102, and the pinhole 1103, and then reaches to the photodetector 1104. The light beam 114, serving as an observation beam, is propagated to the microscopy lens set 8.

[0064] In this embodiment, the detecting system is of programmable control, so as to separately process the captured signal, control the incident angle, and compute the refractive indices, wherein the main program can be constructed in a graphic manner. The laser light source 101 can be activated by sending a TTL adjusting signal from the main program to the laser driver. Moreover, the phase delay under measuring the amplitude can be adjusted to zero by using the phase modulator 2 of the feedback control system. The light beam 100 is split by the beam-splitter 104 into the referencing beam and sampling beam. The referencing beam and the sampling beam are led to linear po-

larizer 106, liquid crystal modulator 2, and the optical beam expander 804. The light intensity and polarization state of the measuring light beam 120 also provide a reference of the light intensity and polarization state of the sampling beam 110 for control. The detection method is splitting the light beam 120 into two light beams by using beam-splitter 31. One light beam 121 is directly propagated to the photodetector 304, and another light beam 122 transverses through the polarizer 302 and is propagated to the photodetector 303. At this time, the main program reads the light intensity values on the photodetector 303, 304 through the signal acquisition card 305, 306.

[0065] The sampling light beam 110 can enter the variable incident angle optical set 6. Due to the optical properties of the penta prism 601, it is assured that the refractive light beam 111 is perpendicular to the light beam 110 normally incident onto the penta prism. The light beam 111 can also serve as the horizontal incident beam for the concave quasi-paraboloidal reflective mirror 602. In this embodiment, the main program controls the uniaxial displacement stage 605 of the penta prism 601 through the motion control card 604, the limited switches 607, 608, so as to move back-and-forth along the Z-axis and then control the incident angle of the light beam 1111 on the tested sample. The variable incident angle optical set 6 is used to allow the light beam 111 to transverse through the substrate 12 of biochip to the coated metal film at the specific location. A total reflection occurs at the interface between the substrate for the biochip and the coated metal film, so that a sampling light beam 1112 is formed. Under the adjustment of the incident angle with the range of total reflection, the surface plasmon wave on the interface has changed. These changes are related to the thickness and re-

fractive indices of the tested sample, that is, the size of the bio-molecules and the concentration of the tested sample.

[0066] Due to the combination of the concave quasi-paraboloidal mirror 602 and the concave quasi-spherical mirror 603, the sampling light beam 1112 is normally incident on to the concave quasi-spherical mirror 603 and is reflected as the incident light beam 1121 on the backward light path. The center point of the quasi-spherical mirror 603 is, for example, located on the measuring point. It transverses along the same light path of the light beam 1112 and enters the substrate 12 of the biochip. At the same measuring point to cause a reflection, the backward light beam 1122 is amplified for twice, so that the resolution of the plasma resonant angle is improved, when comparing with convention structure.

[0067] In the embodiment, the microscopy lens set 8 serves as a camera device by including the lens set 801, the CCD array 802, and the frame-grabbing card 803. The microscopy lens set 8 can be used to observe and adjust the measuring point on the sliding block. The microscopy lens set 8 uses the same laser light source 101 for observing light source and the sampling light beam 110. In this manner, there is no need of an extra light source. Moreover, the microscopy lens set 8 read the image at the measuring point through the frame-grabbing card 803. When it is connected to computer or monitor, image can be instantly observed and it can also be used as an autocollimator for the sampling light beam 110.

[0068] By using the location of the penta prism associating with the quasi-paraboloidal mirror, the angle of the section can be determined. As the incident light transverses through the penta prism, the quasi-paraboloidal mirror would reflect the

light beam to the biochip. The reflected light beam then transverses back to the penta prism and is led to a pinhole through a splitting mirror. The purpose of the arrangement is to filter out the image losing its focus, so as to achieve the section performance. Then a photodetector is used to measure the light intensity. This is the process for point measurement. By using the micro-shift platform of the biochip associating with the spatial mapping technology of the invention, it is possible to scan on the XY plane, wherein the micro-displacement stage is moving along the Z axis for performing section. When the image for the section incorporate to the technology of three-dimensional image reconstruction, the configuration of the bio-molecules on the biochip can be displayed. This allows to measure static property at the whole area on the protein chip and antibody or antigen.

Third Embodiment

[0069] A third subsystem according to the evanacent wave theory is depicted below. FIGs. 7A-7B are drawings, schematically illustrating a conventional optical configuration for theory of total reflection evanacent wave excitation. According to the conventional principle, the invention designs a novel system. In the multifunctional opto-electronic biochip detection system of the invention, under the first subsystem, a polarizer is used to adjust the sampling light beam into a p wave. The variable incident angle optical set is used to adjust, so as to cause the sampling light path and the signal light path to be either separating or in common, so as to achieve an angle modulation . This results in two different designs for the amplitude surface plasmon resonance detection. If a lens set of beam expander for expanding the sampling area, then a photo tun-

neling microscope (PTM) is formed. The above three types of design are based on the evanacent wave theory. The plasma signal detector and the PTM can be activated by switching some elements of the multifunctional opto-electronic biochip detection system. The subsystem includes several units as follows.

[0070] A linear polarized light source set includes a visible light source, an attenuator for modulating light intensity, and a linear polarization member. The light source includes, for example, light emitted diode (LED) or laser diode. The linear polarization member includes, for example, a dichroic linear polarizer, a linear polarizer, or a polarizing means for polarizing light.

[0071] A phase modulating unit having capability for modulating the phase includes a compensator, a liquid crystal phase modulator, or a photoelastic phase modulator. The phase modulating unit is used to produce a light with various polarization state.

[0072] An optical beam expander with a lens set is used to expand the area of the sampling point.

[0073] A referencing beam optical analysis unit includes an non-polarizing beam-splitter, an analyzer, and at least two photodetectors.

[0074] A variable incident angle optical set includes a quasi-paraboloidal mirror, a quasi-spherical reflective mirror, and a uniaxial displacement stage with feedback control for loading a prism set. The sample light beam on the measuring point has at least one back-and-forth reflection. The prism set includes, for example, a penta prism or a triangular prism, or even includes a reflector. Function of the variable incident an-

gle optical set is to adjust an incident angle of the incident light beam onto an interface between the substrate of the biochip 12 and the coated metal film.

[0075] An optical signal detecting unit has at least a photodetector. The photodetector includes, for example, a photodioide or a linear array of CCD. The optical signal detecting unit can separately associate with a lens set or analyzer to accomplish the detecting function.

[0076] A microscope lens set has a lens set with high power, and an array of CCD, so as to serve as a camera that is used to monitor the reacting phenomenon of biomolecules.

First embodiment for the third subsystem

[0077] This embodiment is an amplitude surface plasmon resonance detection system. FIG. 8 is a layout drawing, schematically illustrating a third subsystem configuration with confocal image scanning function in the multifunctional opto-electronic biomedical detection system, according a first embodiment of the invention. In FIG. 8, the light beam 100 transverses through the attenuator 102, the reflector 103, and the non-polarizing beam-splitter 104, and then is split into two light beams. One beam transverse along the light path 120 and then transverses through the reflective mirror 105, the polarizer 106, the phase modulator 2, the referencing optical analysis unit 3, so that the light propagation is accomplished. Another light transverses along the light path 110 through the non-polarizing beam-splitter 104. After splitting, the light beam continuously transverses through the polarizer 106, the phase modulator 2, so that the p-state polarizing wave of the sampling light beam 110 on the biochip is adjusted and then

enters the variable incident angle optical set 6. The light beam at the specific detection point of the substrate 12 is reflected to a photodetector 609.

[0078] In the embodiment, the laser light source 101 can be activated by sending a TTL modulating signal to the laser driver. Moreover, the liquid crystal phase modulator 2 used in feedback control can adjust the phase delay to zero under the amplitude measuring manner. The light beam 100 is split into the reference light beam and the sampling light beam by the beam-splitter 104. Then the reference light beam and the sampling light beam are led through the polarizer 106 and the liquid crystal phase modulator 2. The results of the light intensity and polarization state of the reference light beam 120 are used as references for controlling the light intensity and polarization state of the sampling light beam 110. The detection method includes using the beam-splitter 31 to split the reference light beam 120 into two light beams 121, 122. The light beam 121 is directly propagated to the photodetector 304, and the light beam 122 transverses through the analyzer 302 and then propagated to the photodetector 303. In the mean time, the system main program read the light intensity stored on the photodetector 303, 304 through the signal acquisition card 305, 306.

[0079] The sampling light beam 110 can enter the variable incident angle optical set 6. Due to the optical properties of the penta prism 601, it is assured that the refractive light beam 111 is perpendicular to the light beam 110 normally incident onto the penta prism. The light beam 111 can also serve as the horizontal incident beam for the concave quasi-paraboloidal reflective mirror 602. In this embodiment, the main program controls the uniaxial displacement stage 605 of the penta prism 601 through the motion control card 604, the limited switches 607, 608, so as to move back-and-forth

along the Z-axis and then control the incident angle of the light beam 1111 on the tested sample. The variable incident angle optical set 6 is used to allow the light beam 111 to transverse through the substrate 12 of biochip to the coated metal film at the specific location. A total reflection occurs at the interface between the substrate for the biochip and the coated metal film, so that a sampling light beam 1112 is formed. Under the adjustment of the incident angle with the range of total reflection, the surface plasmon wave on the interface has changed. These changes are related to the thickness and refractive indices of the tested sample, that is, the size of the bio-molecules and the concentration of the tested sample.

[0080] In this embodiment, the concave quasi-paraboloidal mirror 602 on the XZ plane has focusing capability, and on the Y direction has uniform cross-section shape. When the light beam 110 is reflected by the concave quasi-paraboloidal mirror 602 to the substrate 12 of the biochip, it would be focused on the coated metal film. The reflected light 1112 is incident to a planar light intensity photodetector 609, so that several measuring points can be parallel measured to observe the variation of the surface plasmon resonant angle.

Second embodiment for the third subsystem

[0081] This embodiment is an amplitude surface plasmon resonance detection system. FIG. 9 is a layout drawing, schematically illustrating a third subsystem configuration with confocal image scanning function in the multifunctional opto-electronic biomedical detection system, according a second embodiment of the invention In FIG. 9, the light beam 100 transverses through the attenuator 102, the reflector 103, and the

non-polarizing beam-splitter 104, and then is split into two light beams. One beam transverses along the light path 120 and then transverses through the reflective mirror 105, the polarizer 106, the phase modulator 2, the referencing optical analysis unit 3, so that the light propagation is accomplished. Another light transverses along the light path 110 through the non-polarizing beam-splitter 104. After splitting, the light beam continuously transverses through the polarizer 106, the phase modulator 2, so that the p-state polarizing wave of the sampling light beam 110 on the biochip is adjusted and then enters the variable incident angle optical set 6. The light beam at the specific detection point of the substrate 12 is reflected back-and-forth for twice and then forms the backward light beam 112, which transverses back along the sampling light path 110 and propagates to non-polarizing beam-splitter 4, 7. After that the light beam 112 is further split into two light beams 113, 114. The light beam 113 transverses through the analyzer 1101 and propagates to the photodetector 1104. The other beam 114 directly propagates to the microscope lens set 8.

[0082] In this embodiment, the detecting system is of programmable control, so as to separately process the captured signal, control the incident angle, and compute the refractive indices, wherein the main program can be constructed in a graphic manner. The laser light source 101 can be activated by sending a TTL adjusting signal from the main program to the laser driver. Moreover, the phase delay under measuring the amplitude can be adjusted to zero by using the phase modulator 2 of the feedback control system. The light beam 100 is split by the beam-splitter 104 into the referencing beam and sampling beam. The referencing beam and the sampling beam are led to linear polarizer 106, liquid crystal modulator 2, and the optical beam expander 804. The light

intensity and polarization state of the measuring light beam 120 also provide a reference of the light intensity and polarization state of the sampling beam 110 for control. The detection method is splitting the light beam 120 into two light beams by using beam-splitter 31. One light beam 121 is directly propagated to the photodetector 304, and another light beam 122 transverses through the polarizer 302 and is propagated to the photodetector 303. At this time, the main program reads the light intensity values on the photodetector 303, 304 through the signal acquisition card 305, 306.

[0083] The sampling light beam 110 can enter the variable incident angle optical set 6. Due to the optical properties of the penta prism 601, it is assured that the refractive light beam 111 is perpendicular to the light beam 110 normally incident onto the penta prism. The light beam 111 can also serve as the horizontal incident beam for the concave quasi-paraboloidal reflective mirror 602. In this embodiment, the main program controls the uniaxial displacement stage 605 of the penta prism 601 through the motion control card 604, the limit switches 607, 608, so as to move back and forth along the Z-axis and then control the incident angle of the light beam 1111 on the tested sample. The variable incident angle optical set 6 is used to allow the light beam 1111 to transverse through the substrate 12 of biochip to the coated metal film at the specific location. A total reflection occurs at the interface between the substrate for the biochip and the coated metal film, so that a sampling light beam 1112 is formed. Under the adjustment of the incident angle with the range of total reflection, the surface plasmon wave on the interface has changed. These changes are related to the thickness and refractive indices of the tested sample, that is, the size of the bio-molecules and the concentration of the tested sample.

[0084] Due to the combination of the concave quasi-paraboloidal mirror 602 and the concave quasi-spherical mirror 603, the sampling light beam 1112 is norm incident on to the concave quasi-spherical mirror 603 and is reflected as the incident light beam 1121 on the backward light path. It transverses along the same light path of the light beam 1112 and enters the substrate 12 of the biochip. At the same measuring point to cause a reflection, the intensity of backward light beam 1122 is modulated for twice, so that the resolution of the surface plasmon resonant angle is improved, when comparing with convention structure.

[0085] In the embodiment, the microscopy lens set 8 serves as a camera device by including the lens set 801, the CCD array 802, and the frame-grabbing card 803. The microscopy lens set 8 can be used to observe and adjust the measuring point on the sliding block. The microscopy lens set 8 uses a same laser light source 101 for observing light source and the sampling light beam 110. In this manner, there is no need of an extra light source. Moreover, the microscopy lens set 8 read the image at the measuring point through the frame-grabbing card 803. When it is connected to computer or monitor, image can be instantly observed and it can also be used as an autocollimator for the sampling light beam 110.

Third embodiment for the third subsystem

[0086] This embodiment is photon tunneling microscope detection system. FIG. 10 is a layout drawing, schematically illustrating a third subsystem configuration with photon tunneling scanning microscope in the multifunctional opto-electronic biomedical detection system, according to a third embodiment of the invention. In FIG. 10,

the light beam 100 transverses through the attenuator 102, the reflector 103, and the non-polarizing beam-splitter 104, and then is split into two light beams. One beam transverses along the light path 120 and then transverses through the reflective mirror 105, the polarizer 106, the phase modulator 2, the referencing optical analysis unit 3, so that the light propagation is accomplished. Another light transverses along the light path 110 through the non-polarizing beam-splitter 104. After splitting, the light beam continuously transverses through the polarizer 106, the phase modulator 2 and an optical beam expander 804, so that the sampling light beam 110 enters the variable incident angle optical set 6. The light beam at the specific detection point of the substrate 12 is led to transverse back-and-forth for twice, and then form the backward light beam 112, which transverses in opposite direction along the same light path of the sample light beam and propagates to the non-polarizing beam-splitters 4, 7. The light beam 112 is further split into two light beams 112, 113. The light beam 113 transverses through the analyzer 1101 and reaches the photodetector 1104. The other light beam 114 directly transverses to the microscope lens set 8.

[0087] In the embodiment, the laser light source 101 can be activated by sending a TTL modulating signal to the laser driver. Moreover, the liquid crystal phase modulator 2 used in feedback control can adjust the phase delay to zero under the amplitude measuring manner. The light beam 100 is split into the reference light beam and the sampling light beam by the beam-splitter 104. Then the reference light beam and the sampling light beam are led through the polarizer 106 and the liquid crystal phase modulator 2. The results of the light intensity and polarization state of the reference light beam 120 are used as references for controlling the light intensity and polarization

state of the sampling light beam 110. The detection method includes using the beam-splitter 31 to split the reference light beam 120 into two light beam 121, 122. The light beam 121 is directly propagated to the photodetector 304, and the light beam 122 transverses through the analyzer 302 and then propagated to the photodetector 303. In the mean time, the system main program read the light intensity stored on the photodetector 303, 304 through the signal acquisition card 305, 306.

[0088] The sampling light beam 110 can enter the variable incident angle optical set 6. Due to the optical properties of the penta prism 601, it is assured that the refractive light beam 111 is perpendicular to the light beam 110 normally incident onto the penta prism. The light beam 111 can also serve as the horizontal incident beam for the concave quasi-paraboloidal reflective mirror 602. The main program controls the uniaxial displacement stage 605 of the penta prism 601 through the motion control card 604, the limit switches 607, 608, so as to move back-and-forth along the Z-axis and then control the incident angle of the light beam 1111 on the tested sample. The variable incident angle optical set 6 is used to allow the light beam 1111 to transverse through the substrate 12 of biochip to the coated metal film at the specific location. A total reflection occurs at the interface between the substrate for the biochip and the coated metal film, so that a sampling light beam 1112 is formed. Under the adjustment of the incident angle with the range of total reflection, the surface plasmon wave on the interface has changed. These changes are related to the thickness and refractive indices of the tested sample, that is, the size of the bio-molecules and the concentration of the tested sample.

[0089] In this embodiment, the concave quasi-paraboloidal mirror 602 on the XZ plane has focusing capability, and on the Y direction has uniform cross-section shape. When the light beam 110 is reflected by the concave quasi-paraboloidal mirror 602 to the substrate 12 of the biochip, it would be focused on the coated metal film. The reflected light 1112 is incident to a planar light microscope 609, which includes a lens set, a CCD array and an frame-grabbing card to serve as an camera. It has function to observe and adjust the measuring points on the biochip. The microscope 609 and the sampling light beam 110 use the same laser source 11, so that there is no need an extra light source. Moreover, the microscope 609 uses the frame-grabbing card to read the image on each measuring point. When the microscope 609 is connected to a computer or a monitor, the image can be instantly observed. According to the image shade, the configuration of bio-molecules on the biochip can be reconstructed. The measurements of the whole area static property on the relation between protein chip, antibody, and antigen can also be used as an autocollimator for the sampling light beam 110. As a result, the multiple sampling points can be parallel measured about the thickness and refractive indices of the sample.

Fourth Embodiment

[0090] A fourth subsystem of the invention is a design integrated with Michaelson interferometer configuration. FIG. 11 is a drawing, schematically illustrating a conventional Michaelson interferometer. The multifunctional opto-electronic biochip detection system of the invention includes a built-in optical interferometer, which is a novel design to integrate various advantages into one. It includes an optical inter-

ferometer shown in FIG. 12, an optical coherence tomography shown in FIG. 13. And a laser Doppler vibrometer/interferometer shown in FIG. 14. Since the invention has achieved the high resolution, cross-sectional perspective view, and dynamic measurement, the invention is suitable for use in biology, medicine, and chemical reaction, which includes both the suitability of two frames of BIA an ELISA. The above functions with respect to the subsystem can be performed by switching a few elements. The fourth subsystem includes several units as follows.

[0091] A linear polarized light source set includes a visible light source, an attenuator for modulating light intensity, and a linear polarization member. The light source includes, for example, light emitted diode (LED) or laser diode. The linear polarization member includes, for example, a dichroic linear polarizer, a linear polarizer, or a polarizing means for polarizing light.

[0092] A phase modulating unit having capability for modulating the phase includes a compensator, a liquid crystal phase modulator, or a photoelastic phase modulator. The phase modulating unit is used to produce a light with various polarization states.

[0093] An optical beam expander with a lens set is used to expand the area of the sampling point.

[0094] A referencing beam optical analysis unit includes an non-polarizing beam-splitter, an analyzer, and at least two photodetectors.

[0095] An interferometer light path control unit has a phase adjusting driver and a light path adjusting element.

[0096] A variable incident angle optical set includes a quasi-paraboloidal mirror, a quasi-spherical reflective mirror, and a uniaxial displacement stage with feedback control for loading a prism set. The prism set includes, for example, a penta prism or a triangular prism, or even includes a reflector. The function of the variable incident angle optical set is to adjust an incident angle of the incident light beam onto the biochip.

[0097] A Doppler signal analyzing unit includes a 1/2 wave plate, an non-polarizing beam-splitter, and two intensity photo-detecting sets. Each of the intensity photo-detecting set includes a polarizer and two intensity photodetectors.

[0098] An interferometric signal analyzing unit includes an analyzer and a photodetector. The photodetector includes, for example, a light emitted diode, a linear array of CCD.

[0099] A microscope lens set has a lens set with high power, and an array of CCD, so as to serve as a camera that is used to monitor the reacting phenomenon of biomolecules.

[0100] FIG. 12 is a layout drawing, schematically illustrating a fourth subsystem configuration with phase shift interference microscope in the multifunctional optoelectronic biomedical detection system, according the embodiment of the invention. In FIG. 12, the light path is depicted. The light beam 100 transverses through the attenuator 102, the reflector 103, and the non-polarizing beam-splitter 104, and then is split into two light beams. One beam transverses along the light path 120 and then transverses through the reflective mirror 105, the polarizer 106, the phase modulator 2, the referencing optical analysis unit 3, so that the light propagation is accomplished. Another light transverses along the light path 110 through the non-polarizing beam-splitter 104.

After traveling through the beam-splitter 104, the light beam also transverses through the linear polarizer 106, the phase modulator 2, the optical beam expander 804, and then is split into two light beams 111 and 131 by the non-polarizing beam-splitter 4. The light beam 111 serves as a sampling light beam to measure the surface configuration used in the interferometer. The light beam 131 serves as an interference light beam for measurements of phase variation.

[0101] the sampling light beam 111 is incident onto the variable incident angle optical set 6, and transverses back and forth for twice at the specific measuring point on the substrate 12 of the biochip, and then a backward light beam 112 is formed. The backward light beam 112 transverses back along the light path of the sampling beam 110, and reaches to the non-polarizing beam-splitter 4. The light beam 131 through, for example, a Febry-Perot device, can be adjusted to have the same total light path as that of the light path 112, so that after the light beam 132 and the light beam 112 transverse through the non-polarizing beam-splitter 4, an interference occurs between the transmitting and reflection components. This interfered light beam is further split into two light beams 113, 114 by the non-polarizing beam-splitter 7. The light beam 113 propagates to the to the photodetector 1104 through the analyzer 1101, and the light beam 114, serving as an observation light beam, propagates to the microscope lens set 8.

[0102] The invention is under programmable control to separately process capturing signals, control the incident angle, and compute the index of reflection for the tested sample, wherein the main control program is executed by a graphic user interface. The laser light source unit 1 can be activated by issuing a TTL modulation signal from the main program to the laser driver, so as to modulate the detecting signals. Moreover,

in order to use the feedback control system to control the liquid crystal phase modulator 2, the main program properly sends a voltage square wave to the liquid crystal, so as to control the phase delay. However, as the liquid crystal plate is used as the phase modulator, a birefringence phenomenon occurs under the driving of voltage. As a result, the phase delay angle is nonlinear for the transmitting light intensity. The absorption property is also nonuniform. The light beam 100 is then necessary to be split by the beam-splitter 104 to for the referencing light beam 104 and the sampling beam. The referencing light beam and the sampling light beam are led to transverse through the linear polarizer and liquid crystal phase modulator 2, and then results of intensity and polarization state of the referencing light beam 120 are used as the references for the sampling light beam. The detection manner is using the beam-splitter 301 to split the referencing light beam 120 into two light beams 121, 122. The light beam 121 directly propagates to the photodetector 304, and another light beam 122 transverses through the analyzer 302 and reaches to the photodetector 303. At this situation, the system main program reads the intensity stored in the photodetectors 303, 304 through the signal acquisition card.

[0103] The sampling light beam 110 can enter the variable incident angle optical set 6. Due to the optical properties of the penta prism 601, it is assured that the refractive light beam 111 is perpendicular to the light beam 110 normally incident onto the penta prism. The light beam 111 can also serve as the horizontal incident beam for the concave quasi-paraboloidal reflective mirror 602. The main program controls the uniaxial displacement stage 605 of the penta prism 601 through the motion control card 604, the limited switches 607, 608, so as to move back-and-forth along the Z-axis and

then control the incident angle of the light beam 1111 on the tested sample. The variable incident angle optical set 6 is used to allow the light beam 1111 to transverse through the substrate 12 of biochip to the coated metal film at the specific location. A total reflection occurs at the interface between the substrate for the biochip and the coated metal film, so that a sampling light beam 1112 is formed. The concave quasi-paraboloidal reflective mirror 602 and the concave quasi-spherical reflective mirror 603 are associated with each other, so that the reflection light of sampling light beam 1112 is normal incident onto the concave quasi-spherical reflective mirror 603 and then a light beam 1121 is formed. The light beam 1121 transverses back along the original light path of the sampling light beam 1112 and then enters the substrate 12 of the biochip. A reflection occurs at the detecting point, so that phase of the reflected light beam 1122 has been changed twice. The phase variation is related to the surface configuration of bio-molecules of tested sample on the biochip, whereby the system configuration of the invention has higher in resolution than the conventional interferometer.

[0104] As a five-step phase shifting manner is used to perform the optical interference, the phase change of the reflection light beam 1122 is to be captured. In the foregoing description, under the reflection condition, the voltage control driver 501 has changed the light path of the light beam 132. The light beams 132 and the light beam 112 interfere and can generate five different phases. The DCT reconstruction method is used to backward calculate the phase value of the backward light beam 112.

[0105] In the embodiment, the invention includes a lens set 801, an array CCD 802, and an frame-grabbing card 803 to have the function of camera. The microscope lens set 8 is used to observe and adjust the measuring point on the sliding plate. The

observing light source and the sampling light beam 110 are from the laser source 11, so that the system does not need extra light source. The microscope lens set 8 read the image at the measuring point through the frame-grabbing card 803. The image can be instantly observed when it is connected to computer or monitor, and simultaneously serves as an autocollimator for the sampling light beam 110.

[106] FIG. 13 is a layout drawing, schematically illustrating a fourth subsystem configuration with optical coherence tomography technology in the multifunctional opto-electronic biomedical detection system, according the embodiment of the invention. In FIG. 13, a polarized light source unit 1 includes alight source 101, intensity modulator 102, a reflective mirror 103, a non-polarizing beam-splitter 104, a reflective mirror 105 and a polarizer 106. The light source 101 produces a light beam 100, which transverses through the intensity modulator 120 and the reflective mirror 103 and reaches the beam-splitter 104. The beam-splitter 104 splits the light beam 100 into a measuring light beam 110 and a referencing light beam 120. The measuring light beam 110 and a referencing light beam 120 transverse through the polarizer 106 and enter the phase modulating unit 2. The phase modulating unit 2 includes a liquid crystal associating with feedback control system. Then, a referencing light beam 120 enters a reference analyzing unit 3, which includes two beam-splitters 301, 302 and two photodetectors 303, 304. The referencing light beam 120 is split by the beam-splitter 301 into two light beams 121, 122 that are respectively detected by the photodetectors 304 and 303. The measuring results are used to adjust the light intensity of the measuring light beam 110. After the measuring light beam 110 transverses to the beam-splitter 4, a referencing light beam 130 is split out. The referencing luminous light beam 130 enters the

light path adjusting unit 5 and transverses through a Febry-Perot reflection cavity 504, and then reaches the reflective mirror 502. The reflective mirror can produce a referencing wave front. After reflection, it transverses through the Febry-Perot reflection cavity 504 again and leaves the light path adjusting unit 5. The residual portion of the measuring light beam 110 enters the variable incident angle optical set 6, and reaches to the penta prism 601. The penta prism 601 refracts the light beam into the paraboloidal mirror 602. The paraboloidal reflective mirror 603 reflects the light to the substrate 12 of the biochip. The light beam can enter the substrate 12 by a specific measuring point, and then is reflected to the spherical mirror 603 through the substrate 12. The light is reflected to the tested sample on substrate again by the spherical mirror 603 along the same light path. After reflection by the substrate, the light beam leaves the variable incident angle optical set 6. After traveling twice on the tested sample, the measuring light beam 110 and the referencing light beam 130 are superimposed at the beam-splitter 4. It continuously transverses to the beam-splitter 7, which split a portion of the light beam into the image capturing unit 8. The image capturing unit 8 has a lens set 801 and CCD for recording the interference pattern.

[0107] In the foregoing, Febry-Perot reflection cavity 504 can control the light path and its total track of the referencing light beam 130 to provide the same light path as the light beam 110, and further control the points, which can cause the interference pattern, to be located at the desired location with respect to the sectional area of the tested sample. Moreover, the light path adjusting unit includes a voltage driver 501 to control the location of the reflective mirror 502. It is helpful for operation of the 5-step phase shifting procedure. As a result, the phase of the interference pattern is obtained.

The penta prism 601 can be moved up-and-down by a motor, whereby the incident angle of the measuring light beam 110 is changed but the measuring point is still the same.

[0108] The optical mechanical structure of the multifunctional opto-electronic biochip detection system can perform function of the optical coherence tomography. Moreover, the invention can also includes other functional units to enhance the function of the invention, so as to achieve the multifunctional detection system for biology, medical, and chemical reaction.

[0109] FIG. 14 is a layout drawing, schematically illustrating a fourth subsystem configuration with Doppler laser interference technology in the multifunctional opto-electronic biomedical detection system, according the embodiment of the invention. In FIG. 14, another embodiment is designed with a Doppler vibrometer / interferometer. a polarized light source unit 1 includes a light source 101, attenuator 102, a reflective mirror 103, a beam-splitter 104, a reflective mirror 105 and a polarizer 106. The light source 101 produces a light beam 100, which transverses through the intensity modulator 102 and the reflective mirror 103 and reaches the beam-splitter 104. The beam-splitter 104 splits the light beam 100 into a measuring light beam 110 and a referencing light beam 120. The measuring light beam 110 and a referencing light beam 120 transverse through the polarizer 106 and enter the phase modulating unit 2. The phase modulating unit 2 includes a liquid crystal associating with feedback control system. Then, the referencing light beam 120 enters a reference analyzing unit 3, which includes two beam-splitters 301, 302 and two photodetectors 303, 304. The referencing light beam 120 is split by the beam-splitter 301 into two light beams 121, 122 that are re-

spectively detected by the photodetectors 304 and 303. The measuring results are used to adjust the light intensity of the measuring light beam 110. After the measuring light beam 110 transverses to the beam-splitter 4, a referencing light beam 131 is split out. The referencing light beam 131 enters the light path adjusting unit 5 and transverses through a Febry-Perot reflection cavity 504, and then reaches the reflective mirror 502. After reflection, it transverses through the Febry-Perot reflection cavity 504 again and leaves the light path adjusting unit 5.

[0110] The measuring light beam 110 is also split a portion by the beam-splitter 4 to form a measuring light beam 111 which has the same intensity as the light beam 131. The light beam 111 enters the variable incident angle optical set 6, in which the penta prism 601 refracts the light beam into the paraboloidal mirror 602. The paraboloidal mirror 602 reflects the light beam to the substrate 12 and reaches to a specific measuring point. After reflection from the measuring point, the light beam transverses through the substrate and is incident to the spherical mirror 603. After reflection again, the light beam along the same light path enters the substrate at the specific point. The tested sample reflects the light beam. As a result, the light beam leaves the variable incident angle optical set 6.

[0111] The reflection cavity 504 can control a length of the light path of the referencing light beam 130, so as to have the same light path as the measuring light beam 110, and further control the points, which can cause the interference pattern, to be located at the desired location with respect to the sectional area of the tested sample. The light beam 131 transverses through the reflection cavity 504, 1/4 wave plate, and the reflective mirror controlled by the voltage driver, and then a reflection light beam 132 is

formed. The reflection cavity 504 associating with reflective mirrors 502, 505, 506 and the voltage driver 501 are used to control the light beams 131 and the reflection light beam 132 to have the same light path. As a result, the referencing luminous light beam 132 and the measuring light beam 112 before interference can transverse back to the non-polarizing beam-splitter 4 with the same total length of the light path. At the same time, issue of the coherence length of laser light can be solved. The light beams 131, 132 transverses twice through the 1/4 wave plate, causing a polarization state with 90° difference from the measuring light beam 110.

[0112] After reflection twice, the light beam 112 and the light beam 131 meet at the beam-splitter 4 and cause interference. Through the beam-splitter 7, the merged light beam is split into a signal light beam 113 and an observing light beam 114. The signal light beam 113 is led to the signal analyzing unit 9 by the rotation reflective mirror 10. The observing light beam 114 propagates to the microscope lens set 8.

[0113] Returning to the beam-splitter 4 which splits the light beam into two light beams 131 and 132, it can be computed according to the Jones computation rule.

$$(1) \qquad \mathbf{E}_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix} e^{j2\pi ft} \quad \mathbf{E}_2 = \begin{bmatrix} 0 \\ 1 \end{bmatrix} e^{j(2\pi(f+2f_d)t+\phi)} ,$$

where f represent the laser frequency and also indicates the Doppler frequency of the tested sample in motion. ϕ is a light path difference or a relative phase difference due to reflection. The phase difference does not vary with time.

[0114] In the signal analyzing unit 9, due to the fast axis of the 1/4 wave plate 901 is placed along the direction having 45° polarization from the light beam 115. After the light beam 115 transverses through the 1/4 wave plate, a right-handed circular-

polarized light beam and a left-handed circular-polarized light beam are produced. Since the two light beams has four times of Doppler frequency $4f_d$ due to circular rotation. After interference, a circular-polarized light beam with circular frequency is produced, in which the low frequency carries the high frequency. The low frequency is $2f_d$ and the high frequency is 2 $(f\text{-}f_d)$. The interference light beam is formed after traveling through the 1/4 wave plate 901, the non-polarizing beam-splitter 4 splits the light beam into two polarizing light beams P and Q with equal light intensity. The light beam P transverses through a polarizer with 45° polarization. The light beam Q transverses through a polarizer with the polarization direction along the x-axis. These two light beam P and Q are respectively detected by the photodetectors for light intensity. Due to the limitation of the frequency, the light intensity detected by the photodetector varies as the low frequency of $4f_d$. After being converted to voltage and being amplified, a signal with normal shift in phase between two light beams is obtained. This is a sine/cosine signal. The detected signal then forms a Lissajous circle, which can be used for bi-pase identification. This can solve the directional ambiguity in the interferometer, so that the moving direction of the tested sample can be determined.

[0115] Moreover, the microscope lens set 8 uses the frame-grabbing card 803 to read the image at the measuring point. After connection to the computer or monitor, the image can be instantly observed. By the measured gray step of the image, the surface configuration of bio-molecules on the biochip can be reconstructed. The measurements of the whole area static property on the relation between protein chip, antibody, and antigen can also be used as an autocollimator for the sampling light beam 110. As a result,

the multiple sampling points can be parallel measured about the thickness and refractive indices of the sample.

[0116] In the invention, the detection unit for the PQ signal associating with a ultrasonic device to excite the bio-molecules on the biochip through a band width. From dynamic frequency response of the bio-molecule transformation function for the signal detection and the input signal source, the recombination capability between molecules and the bio-molecules can be clearly observed. Since the weight of the bio-molecules is small and the frequency is high, the Doppler vibrometer or interferometer incorporate to ultrasonic exciting mechanism is a very useful tool in biology, medicine and chemical reaction.

[0117] Another embodiment with integration of the third subsystem and the fourth subsystem, using interferometry and phase difference in surface plasmon resonance is described as follows.

[0118] In this embodiment, the invention utilizes a Michaelson interferometer in corporate to the technology of surface plasmon resonance by switching a few elements, so that a novel function to detect the phase difference with surface plasmon resonance is disclosed. The subsystem includes several units as follows.

[0119] A linear polarization light source set includes a single frequency visible light, an attenuator for modulating light intensity and a linear polarization device. The light source includes, for example, LED or laser diode. The linear polarization device includes, for example, a linear polarization film, a linear polarizer or any linear polarizer.

[0120] a phase modulator, having modulating function, includes a compensator, a liquid crystal phase modulator or a photoelastic phase modulator, so as to provide various polarization states.

[0121] A referencing optical analyzing unit includes an non-polarizing beam-splitter, an analyzer, and two photodetector.

[0122] An interference light path control unit includes a driver for changing phase and a light path adjustable device.

[0123] A variable incident angle optical set has a quasi-paraboloidal reflective mirror, a quasi-spherical reflective mirror, and a uniaxial displacement stage that can be controlled by a feedback manner and carry a prism set. The variable incident angle optical set is used to adjust the incident angle of light onto the biochip.

[0124] An optical signal analysis unit has an analyzer and a photodetector. The photodetector includes, for example, an LED or a linear array CCD.

[0125] A microscope lens set includes a camera apparatus having a high power lens set and an array CCD, so as to monitor the reaction situation of bio-molecules on the surface.

[0126] FIG. 15 is a layout drawing, schematically illustrating an integration of the third and the fourth subsystem configurations, wherein the phase detection of the surface plasmon wave under the interferometer can be performed, according another embodiment of the invention. In FIG. 15, the multifunctional opto-electronic biochip detection system is designed as a phase measurement with surface plasmon resonator. The light beam 100 transverses through the attenuator 102, the reflector 103, and the non-polarizing beam-splitter 104, and then is split into two light beams. One beam

transverses along the light path 120 and then transverses through the reflective mirror 105, the polarizer 106, the phase modulator 2, the referencing optical analysis unit 3, so that the light propagation is accomplished. Another light transverses along the light path 110 through the non-polarizing beam-splitter 104. After traveling through the beam-splitter 104, the light beam also transverses through the linear polarizer 106 and the phase modulator 2, and then is split into two light beams 111 and 131 by the non-polarizing beam-splitter 4. The light beam 111 is used as a sampling light beam to measure the surface plasma resonance. The light beam 131 serves as an interference light beam used in capturing phase variation.

[0127] The invention is of programmable control to separately process captured signals, control the incident angle, and compute the index of reflection for the tested sample, wherein the main control program is executed by a graphic manner. The laser light source unit 1 can be activated by issuing a TTL modulation signal from the main program to the laser driver, so as to modulate the detecting signals. Moreover, in order to use the feedback control system to control the liquid crystal phase modulator 2, the main program properly sends a voltage square wave to the liquid crystal, so as to control the phase delay. However, as the liquid crystal plate is used as the phase modulator, a birefringence phenomenon occurs under the driving of voltage. As a result, the phase delay angle is nonlinear for the transmitting light intensity. The light beam 100 is then necessary to be split by the beam-splitter 104 to for the referencing light beam 104 and the sampling beam. The referencing light beam and the sampling light beam are led to transverse through the linear polarizer 106 and the liquid crystal phase modulator 2, and then results of intensity and polarization state of the referencing light beam

120 are used as the references for the sampling light beam 110. The detection manner is using the beam-splitter 301 to split the referencing light beam 120 into two light beams 121, 122. The light beam 121 directly propagates to the photodetector 304, and another light beam 122 transverses through the analyzer 302 and reaches to the photodetector 303. At this situation, the system main program read the intensity stored in the photodetectors 303, 304 through the signal acquisition card.

[0128] The sampling light beam 110 can enter the variable incident angle optical set 6. Due to the optical properties of the penta prism 601, it is assured that the refractive light beam 111 is perpendicular to the light beam 110 normally incident onto the penta prism. The light beam 111 can also serve as the horizontal incident beam for the concave quasi-paraboloidal reflective mirror 602. The main program controls the uniaxial displacement stage 605 of the penta prism 601 through the motion control card 604, the limit switches 607, 608, so as to move back and forth along the Z-axis and then control the incident angle of the light beam 1111 on the tested sample. The variable incident angle optical set 6 is used to allow the light beam 1111 to transverse through the substrate 12 of biochip to the coated metal film at the specific location. A total reflection occurs at the interface between the substrate for the biochip and the coated metal film, so that a sampling light beam 1112 is formed. Within the condition for causing total reflection, the incident angle is changed, so as to trigger a surface plasmon wave on the interface between the substrate 12 and the coated metal film. The P-wave of the reflection light beam 1112 has phase change. This phase change is related to the thickness and refractive indices of the tested sample on the chip, which is also related with the size of bio-molecules and concentration.

[0129] The concave quasi-paraboloidal reflective mirror 602 and the concave quasi-spherical reflective mirror 603 are associated with each other, so that the reflection light beam 1112 of sampling light beam is normal incident onto the concave quasi-spherical reflective mirror 603 and then a light beam 1121 is formed. The light beam 1121 transverses back along the original light path of the reflection light beam 1112 of the sampling light beam and then enters the substrate 12 of the biochip. A reflection occurs at the detecting point, so that phase of the P-wave of the reflected light beam 1122 has been changed twice. Therefore, the resolution of the surface plasma resonance angle has been effectively improved while comparing with the conventional technology.

[0130] In the embodiment, the microscope lens set 8 includes a lens set 801, a CCD array 802, and an frame-grabbing card 803 to have the function of camera. The microscope lens set 8 is used to observe and adjust the measuring point on the sliding plate. The observing light source and the sampling light beam 110 are from the laser source 11, so that the system does not need extra light source. The microscope lens set 8 read the image at the measuring point through the frame-grabbing card 803. The image can be instantly observed when it is connected to computer or monitor, and simultaneously serves as an autocollimator for the sampling light beam 110.

[0131] The invention discloses the multifunctional opto-electronic biochip detection system. The invention not only can perform the surface plasmon resonance techniques, but also can use interferometer to obtain the phase information. The resolution is greatly improved, resulting in a great tool on the biochemical detection system.

[0132] It will be apparent to those skilled in the art that various modifications and variations can be made to the structure of the present invention without departing

from the scope or spirit of the invention. In view of the foregoing, it is intended that the present invention covers modifications and variations of this invention provided they fall within the scope of the following claims and their equivalents.